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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO	
09/058,323	04/09/1998	BEREND HOUWEN	10690/101683	7347	
75	90 07/22/2002				
BRYAN CAV	<del>-</del>		ЕХАМП	EXAMINER	
245 PARK AVENUE NEW YORK, NY 101670034			GABEL, G	GABEL, GAILENE	
			ART UNIT	PAPER NUMBER	
			1641	9.	
			DATE MAILED: 07/22/2002	26	

Please find below and/or attached an Office communication concerning this application or proceeding.

	Application No.	Applicant(s)	
•	1		
Advisory Action	09/058,323	HOUWEN ET AL.	
	Examiner	Art Unit	
TI MAN INO DATE of this communication	Gailene R. Gabel		
The MAILING DATE of this communication			
THE REPLY FILED 13 June 2002 FAILS TO PI Therefore, further action by the applicant is requ final rejection under 37 CFR 1.113 may only be condition for allowance; (2) a timely filed Notice Examination (RCE) in compliance with 37 CFR	ired to avoid abandonment of this either: (1) a timely filed amendmer of Appeal (with appeal fee); or (3)	application. A proper reply to a nt which places the application in	
PERIOD	FOR REPLY [check either a) or b	)]	
a) The period for reply expires 2 months from the			
b) The period for reply expires on: (1) the mailing d no event, however, will the statutory period for re ONLY CHECK THIS BOX WHEN THE FIRST R	eply expire later than SIX MONTHS from th	e mailing date of the final rejection.	er. In
706.07(f).  Extensions of time may be obtained under 37 CFR 1.1 fee have been filed is the date for purposes of determining fee under 37 CFR 1.17(a) is calculated from: (1) the expirat (2) as set forth in (b) above, if checked. Any reply received timely filed, may reduce any earned patent term adjustment	the period of extension and the correspond ion date of the shortened statutory period f by the Office later than three months after	ling amount of the fee. The appropriate extension reply originally set in the final Office action;	sion
1. A Notice of Appeal was filed on A 37 CFR 1.192(a), or any extension thereo			
2. The proposed amendment(s) will not be e	entered because:		
(a) they raise new issues that would requ	uire further consideration and/or se	earch (see NOTE below);	
(b) they raise the issue of new matter (see	ee Note below);		
<ul><li>(c) they are not deemed to place the apprince issues for appeal; and/or</li></ul>	olication in better form for appeal b	y materially reducing or simplifying th	ne
(d) they present additional claims without	ut canceling a corresponding numb	per of finally rejected claims.	
NOTE:			
<ol> <li>Applicant's reply has overcome the following</li> </ol>	ng rejection(s):		
4. Newly proposed or amended claim(s) canceling the non-allowable claim(s).	would be allowable if submitted	in a separate, timely filed amendmen	nt
5. ☐ The a) ☐ affidavit, b) ☐ exhibit, or c) ☐ re application in condition for allowance becomes		n considered but does NOT place the	
6. The affidavit or exhibit will NOT be consid raised by the Examiner in the final rejection		LELY to issues which were newly	
7. For purposes of Appeal, the proposed am explanation of how the new or amended	endment(s) a) will not be entere claims would be rejected is provide	ed or b)⊠ will be entered and an ed below or appended.	
The status of the claim(s) is (or will be) as	follows:		
Claim(s) allowed: NONE.			
Claim(s) objected to: <u>NONE</u> .			
Claim(s) rejected: <u>1-11</u> .			
Claim(s) withdrawn from consideration: A	IONE.		

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10. Other: \_\_\_\_

Briline R. Bahl

8. The proposed drawing correction filed on \_\_\_\_\_ is a) approved or b) disapproved by the Examiner.

9. Note the attached Information Disclosure Statement(s)( PTO-1449) Paper No(s). \_\_\_\_\_.

Continuation of 5. does NOT place the application in condition for allowance because: applicant's argument is not persuasive. Additionally, the claims as recited, fail to obviate the prior art of record.

Application/Control Number: 09/058,323

Art Unit: 1641

#### **DETAILED ACTION**

## Applicant's Response

1. Applicant's response filed 6/13/02 in Paper No. 26 is acknowledged. Currently, claims 1-13 are pending and under examination.

### Rejections Maintained

### Claim Rejections - 35 USC § 102103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 2. Claims 1-3 and 5-9 stand rejected under 35 U.S.C. 102(e) as being clearly anticipated by Kim et al. (US 5,648,225) for reason of record.

Application/Control Number: 09/058,323

Art Unit: 1641

3. Claims 4 and 10-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al. (US 5,648,225) in view of Inami et al. (US 5,298,426) for reason of record.

# Response to Arguments

- 4. Applicant's arguments filed 1/24/02 have been fully considered but they are not persuasive.
- A) Applicant argues that Kim does not describe or suggest "a mixture of the nuclear stain and the monoclonal antibodies in one analytical reagent".

In response, the claimed method does not appear to define such feature: "a mixture of the nuclear stain and the monoclonal antibodies in one analytical reagent".

B) Applicant argues that Kim does not describe or suggest "a mixture of the nuclear stain and the monoclonal antibodies in one method" and does not suggest that the nuclear stain and monoclonal antibodies can exist together.

Contrary to Applicant's argument, Kim discloses that the multipurpose reagent system includes salts and buffers, as well as nuclear stain and antibody against cell surface antigens for use in rapid analysis of a whole blood sample, allowing determination of at least five classes of peripheral white blood cells and nucleated red blood cells (see Abstract and column 6). Further, Kim does, teaches the method as claimed by Applicant. Specifically, Kim teaches how the multipurpose reagent system is used in a method of discriminating and counting between leucocytes and erythroblasts

Page 4

Application/Control Number: 09/058,323

Art Unit: 1641

or nRBCs. Kim teaches adding 1) fluorochrome-conjugated antibodies directed to leucocyte surface antigens, 2) nucleotide fluorescent dye, i.e. ethidium homodimer, and 3) a proper concentration of aldehydes, salts, and buffer, in a multipurpose reagent system, to an anticoagulated blood sample, incubating the mixture, and subjecting the mixture to flow cytometric analysis. The fluorochrome-conjugated antibodies directed to leucocyte surface antigens bind and stain leucocytes. The nucleotide fluorescent dye stains the exposed nuclei of erythroblasts, but does not penetrate the intact white cells, thus allowing quantitative analysis of nucleated red cells. The mixture of aldehydes, non-quaternary mono-ammonium salt, and buffer permeabilizes, i.e. lyses, the erythroblasts while maintaining the integrity of the fixed white blood cells. Electronic signals from scattered light collected from different angles and fluorescence intensities are plotted as two-dimensional plots in column 6, lines 31-46 and also Figure 3. Given that Kim et al. teaches all the limitations recited in the rejected claims, it is maintained that claims 1-3 and 5-9 are anticipated by Kim. As recited, no patentable distinction is seen between the .

C) Applicant argues that the combination of the teaching of Kim and Inami does not suggest the affirmative and manipulative steps taken with respect to the two signals appearing in Applicant's claims such as detecting, analyzing, and discriminating.

Applicant also argues that there is no suggestion and motivation to combine the teaching of Kim and Inami and that Examiner's explanation of the motivation supporting the combination underlying the rejection is insufficient.

Art Unit: 1641

In response, the affirmative and manipulative steps taken with respect to the two different signals incorporating the detection, analysis, and discrimination of two distinct populations by virtue of a nuclear stain at a specific wavelength for one population, and fluorescent labeled cell surface antigen (via monoclonal antibody conjugation) at a specific wavelength for the other population, are a function of flow cytometric analysis and both of Kim and Inami incorporate use of such system to "differentiate" and "classify" populations of cells in their methods. As such, these "manipulative steps" are accounted for, for flow cytometric analysis to work. The simultaneous detection, analysis, and discrimination between populations of cells having distinct stains and labels, manipulation of results obtained, and evaluation of population distribution in a histogram, are precisely the power of flow cytometric analysis.

To reiterate, Kim teaches combining 1) fluorochrome-conjugated antibodies directed to leucocyte surface antigens, 2) nucleotide fluorescent dye, and 3) a proper concentration of aldehydes, salts, and buffer, in a multipurpose reagent system, in order to simultaneously quantitate and discriminate between leucocytes and nucleated RBCs using fluorescent signal analysis by flow cytometry. Inami is incorporated for the "two-reagent system" to substitute for the buffer solution taught by Kim so that the erythroblasts are not lysed, but rather, their cell membranes are increased for permeability of a nucleotide fluorescent dye while the integrity of the cell membrane of leucocyte population is maintained; Inami, likewise, uses fluorescent signal analysis by flow cytometry to differentiate erythroblasts from other leucocytes.

Page 6

Application/Control Number: 09/058,323

Art Unit: 1641

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute the buffer solution of Kim with the two reagent system taught by Inami for use in permeabilizing erythroblasts because Kim specifically taught that integrity and antigenicity of white blood cells need to be optimally maintained during permeabilization, i.e. lysing, of the nRBC's or erythroblasts in order to allow accurate simultaneous quantitation of both populations and Inami specifically taught that the two reagent system eliminates lysing conditions for erythroblasts while maintaining the integrity and shape of WBCs for accurate differentiation of both erythroblast and leucocyte populations.

- 5. For reasons aforementioned, no claims are allowed.
- 6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Application/Control Number: 09/058,323

Art Unit: 1641

Page 7

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gailene R. Gabel July 16, 2002

CHRISTOPHER L. CHIN PRIMARY EXAMINER

GROUP 1800 /64/

Christyle L. Chris